Supplemental Online Content

Moise KJ, Markham KB, Spinella PC, et al. A clinical practice guideline for the management of pregnancy alloimmunized to red blood cell antigens. *JAMA Netw Open*. 2025;8(11):e2544649. doi:10.1001/jamanetworkopen.2025.44649

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods: Methods of Analysis

The development of the guideline was supported by the Department of Defense Combat Casualty Care Research Program, the THOR Network Foundation, and the Allo Hope Foundation. The guideline follows international standards for guideline development and has been reported in accordance with the AGREE II (Appraisal of Guidelines for Research and Evaluation II) reporting checklist.[1,2]The guideline panel comprised experts in the fields of trauma surgery, emergency medicine, anesthesiology, transfusion medicine, obstetrics, maternal fetal medicine, hematology, pathology, neonatology, and pediatrics. Four workgroups were created and leaders recruited for each: (i) trauma and transfusion; (ii) hematology; (iii) maternal and fetal medicine, and (iv) neonatal and pediatric management. Work group members were recruited by the work group leaders from 11 organizations: The American Association for the Surgery of Trauma (AAST), ACS-Committee on Trauma (COT), Eastern Association for the Surgery of Trauma (EAST), Association for the Advancement of Blood and Biotherapies (AABB), Society of Maternal Fetal Medicine (SMFM), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), American Society of Anesthesiologists (ASA), National Association of EMS Physicians (NAEMSP, American College of Emergency Physicians (ACEP), and Combat Casualty Care Research Program (CCCRP). Each workgroup had access to a bioethicist and at least two patient advocates.

Each work group member completed a standardized form to declare conflicts of interest. One of the organizing committee members adjudicated the determination of conflict of interest and decided if an expert panel member needed to be recused from voting on a particular recommendation. Conflicts of interest were fully disclosed and published alongside the guideline.

A team at Johns Hopkins University was commissioned to conduct systematic reviews for questions identified by the four guideline work groups: (i) trauma and transfusion; (ii) hematology; (iii) maternal and fetal medicine, and (iv) neonatal and pediatric management (the first two groups were subsequently combined). Twenty review questions from the work groups were addressed by 17 systematic reviews. Protocols were registered on PROSPERO (CRD42024512662, CRD42024512673, CRD42024512667, CRD42024512247, CRD42024512268, CRD42024512256, CRD42024512261, CRD42024512274, CRD42024512275, CRD42024512271, CRD42024513611, CRD42024513608, CRD42024513606, CRD42024531268, CRD42024513605, CRD42024513614, and CRD42024513615).

Searches were conducted in February 2024 of PubMed and Embase and, for questions related to interventions, the Cochrane Central Register of Controlled Trials (CENTRAL). Searches were developed based on an analysis of medical subject headings (MeSH) and text words from

eligible studies identified *a priori*. An experienced information specialist peer reviewed the search strategies using the Peer Review of Electronic Search Strategies (PRESS) checklist.[3] The reviews had no language restrictions. The reference lists of included articles and relevant reviews were hand searched.

Trials and observational studies were considered. Studies without a comparison group, such as case series or case reports, were identified but were excluded from the systematic review syntheses. Details on the inclusion and exclusion criteria for each research question are presented in Supplement.

All search results were uploaded to a web-based screening tool, PICO Portal (www.picoportal.net). PICO Portal uses machine learning to sort and present first those citations most likely to be eligible, increasing the efficiency of screening without missing relevant citations. Two team members independently screened abstracts until the machine learning prediction of citations eligible for full-text screening reached at least a 95% recall rate. Two reviewers independently screened all full-text articles. Differences regarding eligibility were resolved through consensus adjudication.

Forms were developed in the Systematic Review Data Repository (https://srdrplus.ahrq.gov/) to extract data on study design details, arm details, sample characteristics, and outcomes. One reviewer extracted the data, and a second reviewer confirmed the data for completeness and accuracy. Individual studies were assessed using study design specific tools. We used the Cochrane Risk-of-Bias Tool for Randomized Trials (RoB) to assess the risk of bias of randomized controlled trials,[4] the Newcastle-Ottawa Quality Assessment Scale tool to assess the risk of bias of observational studies,[5] and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the risk of bias of the diagnostic accuracy studies.[6] Two reviewers independently assessed the risk of bias of each study. Differences between reviewers were resolved by consensus adjudication.

A qualitative synthesis was conducted for all questions. Meta-analysis was considered if there were 2 or more studies that were sufficiently similar with respect to key variables (study design, population characteristics, comparisons). Heterogeneity among the studies for each outcome we considered appropriate for quantitative pooling was tested using a standard chi-squared test using a significance level of alpha less than or equal to 0.10. Heterogeneity among studies was also assessed with an I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. A value greater than 50 percent was considered to indicate substantial heterogeneity.[7] We do not report summary estimates if we found high statistical heterogeneity (i.e., I-squared > 75%). For continuous outcomes, mean difference was calculated by using a random-effects model with the DerSimonian and Laird formula.[8] For dichotomous outcomes, a pooled effect estimate was calculated of the relative risk between the study groups, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[8]

eMethods: Methods of Analysis

Based on input from the work group members, the critical outcomes were identified *a priori* for each review question. The certainty of the evidence was assessed for critical outcomes using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methods.[9]

Development of Recommendation Statements

The reports of the systematic reviews were provided to work group members and used to inform development of draft recommendations. The draft recommendations were presented at a public meeting on November 19, 2024. After public comment was incorporated into the draft recommendations, the revised recommendations were presented in a closed guideline meeting on November 20, 2024. Each recommendation was voted on by all work group members with the Delphi method used to determine consensus. Consensus was defined prior to voting as at least 75% agreement. Voting was conducted online using Poll Everywhere. Voting was permitted for 3 rounds of edits. If a recommendation did not achieve consensus after 3 rounds of voting, then that recommendation was considered to have not reached consensus.

Final recommendations that achieved consensus were then edited for grammar and clarity. The organizing committee and work group leaders determined if the edits changed the content of the recommendations. Any content related change led to those recommendations being voted on again by the entire guideline group with the same process and threshold for consensus. The final recommendations and the rationale to support them were then released for public comment from patients contacted via the Allo Hope Foundation and from experts through the 11 associations and societies that were represented within the four work groups.

Role of the Funding Source

The guideline work groups identified the questions for review. The funding source and other supporters had no role in the conduct of the systematic reviews, including in the search, determination of study eligibility, synthesis, grading, or preparation of the systematic review reports.

eTable 1. List of Members of the Working Groups

Trauma/Transfusion Subgroup	Leaders	Members
	Christine Leeper, MD	Alyssa Ziman, MD
	Mark Yazer, MD	Barbara Gaines, MD
		Barbara Gaines, MD
		Bryan Cotton, MD, MPH
		Denis Snegovskikh, MD
		Donald Jenkins, MD
		Frank Guyette, MD
		Jason Sperry, MD
		Jay Malone, MD, MS, PhD
		*COL Jennifer Gurney, MD
		Joseph Sakran, MD, MPA, MPH
		Juan Duchesne, MD
		Katie Shanahan, CPNP
		Nancy Dunbar, MD
		Pampee Young, MD
		Philip Spinella, MD
		Rich Gammon, MD
		Susan Stern, MD
		CAPT Travis Polk, MD
		* Karen Robinson, PhD, MSc
		* Lisa Wilson, ScM
Hematology Subgroup	**Leaders**	**Members**
	Cassandra Josephson, MD	*Andre Cap, MD, PhD
	Jennifer Andrews, MD	Jeanne Hendrickson, MD
		Molly Sherwood
		Paul Ness, MD
		Ross Fasano, MD
		Stella Chou, MD
		* Karen Robinson, PhD, MSc
		* Lisa Wilson, ScM

*Non-voting member

eTable 1. List of members of the working groups

MFM/OB Subgroup	Leader	Members
	Kenneth Moise, MD #	*Anthony Sciscione, DO
		Bethany Weathersby, MEd
		Donna Dizon-Townson, MD
		Jimmy Espinoza, MD, Msc
		Juan González Vélez MD, PhD
		Kara Markham, MD
		Laura Mercer, MD, MBA, MPH
		Leonardo Pereira, MD, M.C.R.
		*Russell Miller, MD
		Alireza Shamshiraz, MD
		*Thomas Trevett, MD
		* Karen Robinson, PhD, MSc
Neonatal/Pediatrics Subgroup	**Leader**	**Members**
	Tim Bahr, MD	Allison Ayapantecatl
		Ravi Patel, MD
		*Robert Christensen, MD
		Sarah Ilstrup, MD
		*Jon Watchko, MD
		Kenneth Moise, MD
		Molly Sherwood
		Jay Malone, MD, MS, PhD
		Philip Spinella, MD
		* Karen Robinson, PhD, MSc
		* Lisa Wilson, ScM

*Non-voting member

Non-voting member on recommendation # 1 and various practice points involving free fetal DNA for determination of the fetal red cell antigen status due to potential conflict of interest

eTable 2. Inclusion and Exclusion Criteria for Each Research Question

Q1. What is the diagnostic accuracy of free fetal DNA in determining the fetal red cell antigen status? Q2. What are the risks and benefits of using free fetal DNA versus amniocentesis/chorion villus biopsy to determine the fetal red cell antigen status?		
Population	• Adult women with a current or previous pregnancy with red cell antibodies known to cause HDFN (i.e., anti-D, anti-C, anti-E, anti-Kell, or anti-Fy[a]) • Singleton pregnancies	
Intervention	• Free fetal DNA for fetal antigen typing	
Comparison	• Neonatal testing for fetal antigen typing (gold standard) • Amniocentesis or chorion villus biopsy for fetal antigen typing	
Outcomes*	• Diagnostic accuracy outcomes ○ **True positive** ○ **False positive** ○ True negative ○ False negative ○ **Frequency of inconclusive results** ○ Sensitivity ○ Specificity	• Risks and benefits outcomes ○ **Pregnancy loss** ○ **Preterm premature rupture of the membranes** ○ **Preterm labor** ○ **Infection** • Increased maternal alloimmunization (change in titer by 4-fold)
Study Design	• Diagnostic accuracy studies • Excludes studies with no original data and meeting abstracts	• RCT • Cohort/observational • Case-control • Cross-sectional • Excludes studies with no original data and meeting abstracts
Timing and Setting	• During pregnancy • Published since 2015 (for updated search) • If there are multiple publications recruiting participants from the same institution/group, then we will analyze only the latest publication.	

Q3. What are the benefits and harms of not using immunomodulation (intravenous immune globulin and/or plasmapheresis) in patients with a history of early-onset severe red cell alloimmunization defined as evidence of fetal severe anemia and/or fetal loss due to HDFN before 24 weeks gestation in a prior pregnancy?	
	Inclusion
Population	• Adult women with a current or previous pregnancy with red cell antibodies known to cause severe HDFN (anti-D, anti-c, Anti-Kell, anti-E) and prior pregnancy loss before 24 weeks of gestation
Interventions	• Antenatal intravenous immune globulin ± plasmapheresis
Comparisons	• No treatment with plasmapheresis or intravenous immune globulin
Outcomes	• Need for any IUT • Gestational age at first IUT • Fetal hemoglobin at first IUT • Number of IUTs • Fetal death • Fetal hydrops • Overall perinatal survival • Maternal complications of immunomodulation
Timing	• During pregnancy and neonatal life up to 28 days of age • Studies from 2000
Type of Study	• RCT • Cohort/observational

eTable 2. Inclusion and Exclusion Criteria for Each Research Question

Q4. What are the benefits and harms of not using immunomodulation in patients with an alloimmunized pregnancy (i.e., patients with severe red cell alloimmunization with a proven or suspected antigen-positive fetus and a titer for anti-D ≥ 512 or a titer for anti-Kell ≥ 64 regardless of prior pregnancy history)?		
	•	
Population	• Adult pregnant women with a current or previous pregnancy with red cell antibodies known to have caused severe HDFN (anti-D, anti-C, anti-Kell, anti-E) AND one or more of the following in a previous pregnancy: ○ Hydrops fetalis prior to 24 weeks ○ Need for IUT at or before 24 weeks gestation ○ Prior pregnancy loss at or before 24 weeks gestation	Adult pregnant women with a current pregnancy with red cell antibodies with a proven or a suspected antigen-positive fetus with an anti-D titer ≥ 512 or an anti-Kell titer ≥ 64
Intervention	• Antenatal intravenous immune globulin and/or plasmapheresis	
Comparison	• No treatment with plasmapheresis or intravenous immune globulin	
Outcomes*	• Need for any IUT • **Gestational age at first IUT** • **Fetal hemoglobin at first IUT** • **Number of IUTs** • Fetal death • Fetal hydrops • **Overall perinatal survival** • Maternal complications of immunomodulation ○ Headache ○ Aseptic meningitis ○ Rash ○ Anaphylaxis ○ Maternal hemolytic anemia • Gestational age at delivery • NICU admission • Length of NICU stay • Neonatal top-up transfusion (timing and frequency) • Neonatal exchange transfusion (timing and frequency)	
Study Design	• RCT • Cohort/observational • Excludes studies with no original data and meeting abstracts	
Timing and Setting	• During pregnancy • Studies from 2000	

eTable 2. Inclusion and Exclusion Criteria for Each Research Question

Q5. What are the benefits and harms of using a critical titer of less than 4 in the Kell alloimmunized pregnancy?	
Population	• Adult women with a current or previous pregnancy with anti-Kell (K1) red cell antibodies with a reported antibody titer • Excluded non-pregnant women and pregnant with antibodies other than anti-Kell
Intervention	• Presence of antibody titers < 4 • Excluded studies that do not stratify outcomes by maternal antibody titer
Comparison	• Presence of antibody titers ≥ 4
Outcomes*	• Receiving IUT in utero (as a marker for significant disease) • **Gestational age at first IUT** • **Fetal hemoglobin at first IUT** • **Number of IUTs** • Receiving plasmapheresis in pregnancy (as a marker for severe disease) • Receiving IVIG in pregnancy (as a marker for severe disease) • Fetal death • Fetal hydrops • Neonatal simple/top-up blood transfusions • Neonatal exchange transfusions • Length of stay in NICU • Length of stay in hospital • **Overall perinatal survival**
Study Design	• Cohort/observational • Case-control • Cross-sectional • Case series • Excluded studies with no original data and meeting abstracts
Timing and Setting	• During pregnancy
Q6. Among women with a current or previous pregnancy with red cell antibodies known to cause HDFN, what are the benefits and harms of starting weekly serial MCA-PSV measurements at 18 weeks gestation versus at 16 weeks gestation?	
Population	• Adult pregnant women with a current or previous pregnancy with red cell antibodies known to cause HDFN
Intervention	• MCA-PSV by Doppler ultrasound at 16 weeks
Comparison	• MCA-PSV by Doppler ultrasound at 18 weeks
Outcomes*	• MCA-PSV by Doppler ultrasound MoM value • **Gestational age at first IUT** • **Fetal hemoglobin at first IUT** • **Number of IUTs** • Gestational age at fetal death • Fetal death • Gestational age at onset of fetal hydrops • Fetal hydrops • **Overall perinatal survival**
Study Design	• RCT • Cohort/observational • Case-control • Cross-sectional • Excluded studies with no original data and meeting abstracts
Timing and Setting	• During pregnancy • Published since 2000

eTable 2. Inclusion and Exclusion Criteria for Each Research Question

Q7. Among women with a current or previous pregnancy with red cell antibodies known to cause HDFN who have received at least one IUT, what are the benefits and harms of stopping IUTs prior to 35 weeks gestation versus stopping at 35 weeks gestation or later?	
Population	• Adult women with a current or previous pregnancy with red cell antibodies known to cause HDFN who have received at least one IUT
Intervention	• Last IUT performed at ≥ 35 weeks gestational age • Excluded studies that did not provide sufficient information regarding the timing of IUT
Comparison	• Last IUT performed < 35 weeks gestational age
Outcomes*	• Fetal death • Gestational age at birth • Hemoglobin at birth • Hematocrit at birth • **Neonatal survival** • Kernicterus • Respiratory distress syndrome • **Days of phototherapy** • **Number of exchange transfusions** • Number of simple transfusions • **Number of days in hospital** • **Number of days in NICU** • Number of "top-up" transfusions • IUT complications, including: ○ Need for emergency caesarean section • Premature rupture of the membranes
Study Design	• RCT • Cohort/observational • Case-control • Excluded studies with no original data and meeting abstracts
Timing and Setting	• In pregnancy and neonatal life up to 3 months of age • Published since 1963
Q8. Among women with a current or previous pregnancy with red cell antibodies known to cause HDFN and an antigen positive fetus who have not received an IUT, what are the benefits and harms of delivery prior to 37-38 weeks gestation?	
Population	• Adult pregnant women with a current or previous pregnancy with red cell antibodies known to cause HDFN and an antigen-positive fetus who have not received IUTs
Intervention	• Delivery at ≥ 37 weeks gestation
Comparison	• Delivery at a gestational age < 37 weeks
Outcomes*	• **Neonatal survival** • Respiratory distress syndrome • **Days of phototherapy** • Number of exchange transfusions • Number of simple transfusions (neonatal hospital course) • **Number of days in hospital** • **Number of days in NICU** • Number of "top-up" transfusions
Study Design	• RCT • Cohort/observational • Excluded studies with no original data and meeting abstracts
Timing and Setting	• In pregnancy and neonatal up to 3 months of age

DNA = deoxyribonucleic acid; HDFN = hemolytic disease of the fetus/newborn; IUT = intrauterine transfusion; IVIG = intravenous immunoglobulin; MCA-PSV = middle cerebral artery peak systolic velocity; MoM = multiples of the median; NICU = neonatal intensive care unit; RCT = randomized controlled trial

* Bolded outcomes indicate critical outcomes (i.e., those which were graded).

eTable 3. Diagnostic Accuracy of Free Fetal DNA for Fetal Antigen Typing, Stratified by Fetal Antigen Type

Author, Year	Total Index Tests	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Inconclusive Results, N (%)	Reference Test
Rhesus D									
Ahmadi, 2016	30	26	0	4	0	100 (NR)	100 (NR)	0 (0)	Cord blood
Bingulac-Popovic, 2021	205	137	3	59	0	100 (97.34 to 100)	95.08 (86.29 to 98.97)	1 (0.5)	Cord blood
Blanco, 2018	111	87	0	24	0	100 (98.85 to 100)	100 (95.83 to 100)	9 (8)	Heel prick blood
Blomme, 2022	205	76	0	42	0	100 (95.3 to 100)	100 (91.6 to 100)	13 (6)	Cord blood
Boggione, 2017	296	209	1	78	0	100 (NR)	98.8 (NR)	8 (3)	Cord blood
de Haas, 2016	32222	15816	225	9739	9	99.94 (99.89 to 99.97)	97.74 (97.43 to 98.02)	NR (0.21)	Cord blood
Duan, 2023	65	55	1	6	0	100 (NR)	85.7 (NR)	3 (5)	Cord blood
Hyland, 2017	647	370	1	226	0	100 (NR)	99.6 (NR)	2 (0.3)	Cord blood
Londero, 2019	133	99	0	34	0	100 (NR)	100 (NR)	0 (0)	Cord blood
Moezzi, 2016	48	45	0	2	0	100 (NR)	100 (NR)	1 (2)	Cord blood
Niguse, 2022	117	104	1	11	1	99.1 (94.8 to 99.9)	91.7 (61.5 to 99.7)	0 (0)	Cord blood
Papasavva, 2016	71	53	0	18	0	100 (NR)	100 (NR)	0 (0)	Postnatal blood

eTable 3. Diagnostic accuracy* of free fetal DNA for fetal antigen typing, stratified by fetal antigen type

Author, Year	Total Index Tests	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Inconclusive Results, N (%)	Reference Test
Pazourkova, 2021	281	95	4	40	5	95 (88.7 to 98.4)	90.9 (78.3 to 97.5)	9 (3)	Cord blood
Picchiassi, 2015	216	116	4	64	9	92.8 (86.9 to 96.2)	94.1 (85.8 to 97.7)	0 (0)	Postnatal blood
Rather, 2019	135	121	1	12	1	99.18 (95.52 to 99.98)	92.31 (63.97 to 99.81)	0 (0)	Cord blood
Sillence, 2015	46	31	1	14	0	100 (NR)	93.3 (NR)	1 (2)	Cord blood
Soothill, 2015	526	267	1	170	0	100 (NR)	99.4 (NR)	63 (12)	Cord blood
Sorensen, 2018	373	233	1	127	0	100 (98.4 to 100)	99.2 (95.7 to 100)	12 (3)	Cord blood
Uzunel, 2022	4293	2685	7	1599	2	99.93 (99.73 to 99.99)	99.56 (99.08 to 99.82)	44 (1)	Cord blood
Vivanti, 2016	416	252	7	148	0	100 (96.9 to 100)	95.2 (90.5 to 97.6)	9 (2)	Cord blood
Yasa, 2020	100	86	0	10	4	95.75 (NR)	100 (NR)	0 (0)	Heel prick blood
Achargul, 2011	120	83	1	31	5	94 (87 to 98)	97 (84 to 100)	0 (0)	Cord blood
Al-Yatama, 2007	54	21	0	28	5	81 (61 to 93)	100 (88 to 100)	0 (0)	Cord blood
Aykut, 2010	29	21	0	8	0	100 (84 to 100)	100 (63 to 100)	0 (0)	CVS/ amniocentesis
Bombard, 2011	443	278	3	121	4	99 (96 to 100)	98 (93 to 99)	37 (8)	Cord blood
Grill, 2009	178	122	2	49	5	94 (91 to 99)	96 (87 to 100)	0 (0)	Cord blood

eTable 3. Diagnostic accuracy* of free fetal DNA for fetal antigen typing, stratified by fetal antigen type

Author, Year	Total Index Tests	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Inconclusive Results, N (%)	Reference Test
Gunel, 2010	19	7	0	12	0	100 (59 to 100)	100 (74 to 100)	0 (0)	Cord blood
Han, 2012	32	24	0	8	0	100 (86 to 100)	100 (63 to 100)	0 (0)	Cord blood
Hromadnikova, 2005	45	24	0	21	0	100 (86 to 100)	100 (84 to 100)	0 (0)	Cord blood
Lo, 1998	57	37	0	18	2	95 (83 to 99)	100 (81 to 100)	0 (0)	Amniocentesis, cord blood
Machado, 2006	81	58	1	15	1	98 (91 to 100)	94 (70 to 100)	6 (7)	Cord blood
Manzanares, 2013	123	73	1	40	1	99 (93 to 100)	98 (87 to 100)	8 (7)	Postnatal blood
Minon, 2008	545	359	1	185	0	100 (99 to 100)	99 (97 to 100)	0 (0)	Amniocentesis, cord blood
Mohammed, 2010	21	12	3	5	1	92 (64 to 100)	63 (24 to 91)	0 (0)	Cord blood
Moise, 2013	342	220	3	96	1	100 (98 to 100)	97 (91 to 99)	22 (6)	Cord blood
Polin, 2013	124	88	0	34	0	100 (96 to 100)	100 (90 to 100)	2 (2)	Postnatal blood
Rouillac-Le Sciellour, 2007	308	229	2	77	0	100 (98 to 100)	97 (91 to 100)	0 (0)	CVS/ amniocentesis, cord blood
Sbarsi, 2012	20	13	0	7	0	100 (75 to 100)	100 (59 to 100)	0 (0)	CVS/ amniocentesis

eTable 3. Diagnostic accuracy* of free fetal DNA for fetal antigen typing, stratified by fetal antigen type

Author, Year	Total Index Tests	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Inconclusive Results, N (%)	Reference Test
Sesarini, 2009	70	34	6	18	2	94 (81 to 99)	75 (53 to 90)	10 (14)	Cord blood
Siva, 2003	28	17	2	4	3	85 (62 to 97)	67 (22 to 96)	2 (7)	CVS/ amniocentesis, cord blood
Turner, 2003	48	30	0	14	4	88 (73 to 97)	100 (77 to 100)	0 (0)	Postnatal blood
Tynan, 2011	148	86	0	62	0	100 (96 to 100)	100 (94 to 100)	0 (0)	Cord blood
Wang, 2009	78	60	5	10	0	100 (94 to 100)	67 (38 to 88)	3 (4)	Cord blood
Zhong, 2001	34	26	0	7	1	96 (81 to 100)	100 (59 to 100)	0 (0)	CVS/ amniocentesis
Zhou, 2005	94	68	0	26	0	100 (95 to 100)	100 (87 to 100)	0 (0)	Cord blood
Rhesus C									
Finning, 2007	57	39	0	15	0	100 (91 to 100)	100 (78 to 100)	3 (5)	CVS/ amniocentesis, cord blood
Gutensohn, 2010	133	66	0	67	0	100 (95 to 100)	100 (95 to 100)	0 (0)	Amniocentesis
Hromadnikova, 2005	41	17	0	24	0	100 (80 to 100)	100 (86 to 100)	0 (0)	Cord blood
Hromadnikova, 2007	27	21	0	6	0	100 (84 to 100)	100 (54 to 100)	0 (0)	Cord blood

Table 3. Diagnostic accuracy* of free fetal DNA for fetal antigen typing, stratified by fetal antigen type

Author, Year	Total Index Tests	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Inconclusive Results, N (%)	Reference Test
Polin, 2013	122	16	0	106	0	100 (79 to 100)	100 (97 to 100)	0 (0)	Postnatal blood
Rhesus E									
Finning, 2007	46	14	0	30	0	100 (77 to 100)	100 (88 to 100)	2 (4)	CVS/ amniocentesis, cord blood
Gutensohn, 2010	100	21	0	79	0	100 (84 to 100)	100 (95 to 100)	0 (0)	Amniocentesis
Hromadnikova, 2005	45	7	0	38	0	100 (59 to 100)	100 (91 to 100)	0 (0)	Cord blood
Hromadnikova, 2007	21	13	0	8	0	100 (75 to 100)	100 (63 to 100)	0 (0)	Cord blood
Polin, 2013	122	13	0	109	0	100 (75 to 100)	100 (97 to 100)	0 (0)	Postnatal blood
KEL 1									
Finning, 2007	68	21	0	43	1	95 (77 to 100)	100 (92 to 100)	3 (4)	CVS/ amniocentesis, cord blood
Li, 2008	32	11	0	19	2	85 (55 to 95)	100 (82 to 100)	0 (0)	Amniocentesis, postnatal blood
Polin, 2013	122	5	0	117	0	100 (48 to 100)	100 (97 to 100)	0 (0)	Postnatal blood

eTable 4. Good Practice Points and Rationales

Recommendation 1: We recommend the use of maternal free DNA to accurately determine the fetal red cell antigen status drawn after 10 wGA in pregnancies complicated by RhD, RhC, Rhc, RhE, Kell or Fy[a] alloimmunization.	
Practice point	**Rationale**
1.1 A patient case review with a Maternal-Fetal Medicine specialist should be strongly considered soon after red cell alloimmunization is diagnosed in a pregnancy. In some cases, a pre-conceptual consultation with a Maternal-Fetal Medicine specialist may be beneficial prior to the patient considering another pregnancy. In the case of a previous transfusion with Rh-positive RBCs or LTOWB, a preconceptual consult in the Rh-negative patient is also indicated. *90.2% Agreement*	Consultation can allow for personalized treatment planning and healthcare team selection, a pertinent step in HDFN management given the known variation in management practices.[10] This may also expedite the process of fetal antigen testing through free DNA, allow for early titer evaluation to assess risk of severe disease, and allow time for referral and insurance approvals in cases where IVIG may be warranted.
1.2 cffDNAtesting should be collected any time after 10 wGA. In many situations it can be included as part of the NIPT (noninvasive prenatal testing) assay for genetic screening offered by some laboratories. *92.7% Agreement*	cffDNA for fetal antigen status in the U.S. has been validated beginning at 10 wGA.[11] Prompt fetal antigen determination is useful to allow for treatment planning and provider referral when warranted, and to reduce maternal anxiety while awaiting determination of the fetal risk of HDFN. National laboratories outside of the U.S. may have different gestational thresholds for determination of fetal antigen status through cffDNA.
1.3: If cffDNA testing reveals an antigen negative fetus, no further surveillance including repeat titers or middle cerebral artery Doppler measurements are indicated for the remainder of the pregnancy. *100% Agreement*	Due to the accuracy of cffDNAtesting, it is unnecessary to continue to monitor a fetus for suspected HDFN. Continued monitoring can impose unnecessary healthcare costs, logistical and financial burden on the patient, and may identify a falsely elevated MCA-PSV Doppler result which can lead to unnecessary intervention with its inherent risks.
1.4: For alloimmunization to red cell antigens other than RhD, RhC, Rhc, RhE, Kell or Fya alloimmunization where maternal free DNA assays are not available, serial maternal titers and MCA Doppler evaluations can be considered once a critical titer of 16 is noted. Amniocentesis to determine the fetal red cell genotype may also be considered after 15 wGA. 87.5% Agreement	Currently, cffDNA is not available for less common antigens known to cause HDFN. In these rare cases, monitoring should occur as if the fetus is antigen positive unless determined otherwise by paternal antigen phenotype or amniocentesis. Amniocentesis should not delay the initiation of an intrauterine transfusion, and for this reason, amniocentesis may be prudent once the antibody titer reaches critical levels or if MCA-PSV Doppler findings begin to rise.

eTable 4. Good Practice Points and Rationales

Recommendation 2a: We recommend the use of IVIG in patients with a documented antigen positive fetus with a history of either fetal anemia or a fetal loss due to HDFN before 24 wGA in a previous pregnancy. Recommendation 2b: We suggest the use of IVIG in patients in a pregnancy with a documented antigen positive fetus and a titer for anti-D of ≥ 512 or a titer for Kell ≥ 64 regardless of prior pregnancy history.	
Practice point	**Rationale**
2.1: A positive fetal antigen status should be documented as early as possible, preferably through maternal free DNA testing prior to initiation of IVIG. However, in some circumstances IVIG may be started while antigen status is pending *91.9% Agreement*	IVIG therapy is associated with maternal complications as well as considerable expense. Its use should be limited to alloimmunized pregnancies where the fetus is at risk for the development of anemia. *However, initiating IVIG while the fetal antigen status is pending is sometimes prudent as it is best initiated prior to 13 wGA (see Practice Point 2.5).*
2.2: Patients should be made aware of the complications of IVIG therapy prior to its initiation including risks for malaise, fatigue, headache, aseptic meningitis, hemolytic anemia, and thrombosis. *100% Agreement*	Headaches are the most common complication of IVIG therapy. Patients should be informed of their onset which typically occurs 6 – 24 hours after infusion. Patients with a history of migraine headaches are at higher risk for aseptic meningitis.[12] Although not a contraindication to the use of IVIG, these patients should be monitored closely.
2.3: The initial dose of IVIG should be administered in an acute care setting such as a hospital or infusion center to monitor for adverse reactions. *100% Agreement*	Anaphylaxis with IVIG is rare but has been reported especially in patients with IgA deficiency. Current recommendations however, do not recommend the routine assessment of IgA levels prior to initiating IVIG therapy.[12]
Recommendation 2a: We recommend the use of IVIG in patients with a documented antigen positive fetus with a history of either fetal anemia or a fetal loss due to HDFN before 24 wGA in a previous pregnancy Recommendation 2b: We suggest the use of IVIG in patients in a pregnancy with a documented antigen positive fetus and a titer for anti-D of ≥ 512 or a titer for Kell ≥ 64 regardless of prior pregnancy history.	
Practice point	**Rationale**
2.4: Dose calculations should be based on the patient's baseline weight with no escalation in dose. A commonly employed dose used is 1 gr/kg weekly. *92.1% Agreement*	IVIG at a dose of 1 gr/kg/week was initially employed in the treatment of pregnancies complicated by alloimmune thrombocytopenia to prevent fetal thrombocytopenia.[13] A dose of 1 gr/kg/week has been adopted for the treatment of HDFN in most reported studies.[14] This is consistent with a recent international Delphi survey that found 75% agreement with this weekly dose without the need for a loading dose.[15]
2.5: Ideally IVIG should be initiated prior to 13 wGA or as early as possible thereafter. *97.4% Agreement*	The primary therapeutic mechanism of IVIG is thought to be related to blockade of the FcRn receptor of the placenta. Since the transplacental transport of maternal IgG begins at 10 -12 wGA,[16]the initiation of IVIG during this time period may result in a greater therapeutic effect in delaying the need for IUTs.[17]

eTable 4. Good Practice Points and Rationales 2a

Practice point	Rationale
2.6: Patients with blood type A, B or AB should be followed with serial hemoglobin measurements to monitor for maternal hemolysis. *94.7% Agreement*	In non-type O patients, the presence of anti-A or anti-B antibodies in IVIG preparations can result in a maternal hemolytic anemia.[18] In one series of 1000 IVIG-treated non-pregnant adults, 16 cases experienced significant hemolysis with 3 requiring red cell transfusions.[19] Maternal hemoglobin checks every 1-2 weeks should be considered.
2.7: Cessation of IVIG therapy should be considered after the initiation of intrauterine transfusion therapy. *97.4% Agreement*	IVIG therapy has been shown to prolong gestation until intrauterine transfusions are necessary. Associated complications and the costs of IVIG merit consideration for discontinuing therapy once IUTs are initiated.
2.8: Plasmapheresis can be considered prior to IVIG in patients with high initial maternal titer (anti-D of ≥ 512 or a titer for Kell ≥ 64). *97.4% Agreement*	Plasmapheresis alone has been used in the treatment of red cell alloimmunization particularly when it is associated with a significant elevation in the maternal titer. Rebound of the titer often occurs soon after the procedure due to a decrement in the maternal circulating IgG pool. Combining IVIG with plasmapheresis has been shown to result in a persistent lowering of the maternal titer.[20] One protocol that has been described involved three double-volume exchanges in a week followed by an IVIG infusion after the third procedure.[20]

eTable 4. Good Practice Points and Rationales

Recommendation 3*:* We recommend that surveillance with middle cerebral artery peak systolic velocity measurements be initiated when the maternal Kell titer is 4 or greater OR there is a history of an affected fetus/neonate in an antecedent pregnancy.	
Practice point	**Rationale**
3.1: If an initial titer is below critical, repeat titers should be performed monthly until 24 wGA, increasing to every 2 weeks thereafter. In some clinical circumstances, a repeat titer may be indicated earlier than this interval if obstetrical circumstances indicate a risk for enhanced alloimmunization (example: genetic amniocentesis, abdominal trauma or placenta abruption). *97.5% Agreement*	Although there is no literature specifically addressing the frequency of antibody titer determination for patients whose initial or most recent Kell titer is <4, increasing frequency of testing to every 2 weeks at 24 wGA allows for closer monitoring and may mitigate the rare occurrence of HDFN occurring at lower titers. More frequent monitoring is also judicious in the setting of events that may result in maternal-fetal hemorrhage with subsequent worsening of the alloimmunization process.
3.2: Serial titers should be performed at the same laboratory since there are variations in methodology. Preferably titers should be run in tandem with the patient's previous titer to detect increases. *100% Agreement*	This recommendation is in line with guidance from the Association for the Advancement of Blood and Biologic therapies (AABB), a recommendation that accounts for the possibility of intra- and inter-observer variability inherent to the techniques employed for antibody titration.[21]
Recommendation 4 We recommend that middle cerebral artery peak systolic velocity (MCA-PSV) measurements be initiated weekly by 16 wGA in patients with red cell antibodies associated with HDFN when there is an antigen positive fetus or antigen unknown fetus once a critical titer threshold has been reached. A critical titer is defined as 16 or greater for most antibodies and 4 or greater for anti-Kell.	
Practice point	**Rationale**
4.1: cffDNA determination of the fetal antigen status should be considered before initiation and/or continuation of MCA-PSV Doppler measurements. *80% Agreement*	There is a roughly 12% false positive rate inherent to the use of MCA-PSV measurements as a screening tool for fetal anemia, the occurrence of which may necessitate invasive intervention with a risk of pregnancy loss or fetal demise.[22] The use of this screening modality should be limited to alloimmunized pregnancies where the fetus is at risk for the development of anemia. Although a false negative cffDNA result using U.S. next generation sequencing assays has not been reported in published studies, shared decision making to include the risks and benefits of invasive testing to determine the fetal antigen status can be considered.[23]
4.2: MCA-PSV measurements should be performed in consultation with a Maternal-Fetal Medicine specialist. 100% Agreement	The management of red blood cell alloimmunization and HDFN is a highly specialized field of fetal medicine. The performance of MCA-PSV measurements should be undertaken according to published guidelines to optimize the sensitivity and specificity of this screening tool,[24] and the interpretation of the results thereof requires nuanced consideration of multiple factors to determine if/when intervention via fetal transfusion or delivery is indicated.[25] Consultation with a Maternal-Fetal Medicine specialist is therefore recommended to optimize outcomes for patients.

eTable 4. Good Practice Points and Rationales

Practice point	Rationale
4.3: Cases involving alloimmunization with anti-D, anti-C, anti-c, anti-E, anti-Kell or anti-Jk[a] antibody and/or a history of a severely affected fetus/neonate in the antecedent pregnancy should be followed with weekly MCA-PSV measurements starting at 15 wGA. In some cases of alloantibodies other than -D, -C, -c, -E, -Kell, -Jk[a,] the clinician and patient may mutually agree to conduct MCA Doppler measurements every two weeks with an intent to escalate to weekly MCAs with a rising trend. Consultation with a Maternal-Fetal Medicine specialist with expertise in red cell alloimmunization should be considered in these cases. *95% Agreement*	Anti-D, anti-C, anti-c, anti-E, anti-Kell, and anti-Jk[a] have the greatest hemolytic potential of the red blood cell antibodies, resulting in higher risks of fetal anemia requiring in utero treatment. The detection of fetal anemia by elevated MCA-PSV Doppler has been reported as early as 15 wGA.[28] In pregnancies with these antibodies, monitoring via weekly MCA-PSV measurements is appropriate to monitor for rapidly developing fetal anemia. For c antibodies with less hemolytic potential such as anti-Fy[a] and anti-M, the risk of HDFN is lower, particularly earlier in gestation, and it may be reasonable to decrease the frequency of monitoring to every 2 weeks.[29] However, more frequent monitoring should be considered if an upward trend in MCA-PSV values is noted as this may indicate an evolving fetal anemia.
4.4: MCA-PSV Dopplers should be performed with proper technique by an experienced sonographer. A minimum of three measurements should be determined when the fetus is in quiescent state with no evidence of breathing movements. As close as possible to a zero-degree angle of insonation should be used. Manual calipers instead of onboard software should be used to calculate the peak systolic velocity. The best measurement should be considered the final value. *97.6% Agreement*	MCA-PSV nomograms were established using the above techniques, and use of proper and strict methodologies is critical to optimizing the accuracy of this screening tool for the diagnosis of fetal anemia.[22,24]
4.5: An MCA-PSV measurement of $\geq$ 1.5 MoM is consistent with moderate to severe fetal anemia warranting cordocentesis and preparation for concurrent intrauterine transfusion within 24 – 48 hours if fetal anemia is detected. In some cases of a borderline elevated MCA-PSV value, a repeat measurement within 24 hours may be considered before intervention. *95.1% Agreement*	If moderate to severe fetal anemia is suspected based upon MCA-PSV measurements, a delay in definitive diagnosis and treatment may lead to worsening anemia, development of fetal hydrops, adverse neurologic sequelae, and even death of the fetus. Survival following IUT is significantly lower in a hydropic fetus.[26] Prompt intervention within 24-48 hours is therefore recommended, although reassessment of MCA-PSV measurements in a short-term interval may be reasonable if values are borderline elevated and/or variable.
4.6: MCA-PSV measurements may be initiated as early as 15 wGA in cases of a high maternal antibody titer or a previous history of early prenatal onset of HDFN. *100% Agreement*	In patients with very high titers and/or a previous history of early onset HDFN, severe fetal anemia may develop in the early second trimester. As screening for moderate to severe anemia and intervention by IUTs is possible, it seems prudent to initiate monitoring for HDFN at 15 wGA this selected high-risk population. Online calculators can be used to convert the measured peak systolic velocity in cm/sec to multiples of the median (MoM): https://www.omnicalculator.com/health/mca.
4.7: Antenatal steroids have been anecdotally associated with a reduction in the MCA-PSV. This effect may last up to 48 hours. For this reason, if a patient is to be referred to a fetal treatment center for possible intrauterine transfusion, steroids should be withheld until the patient arrives at the center. *82.9% Agreement*	A false reduction in MCA-PSV measurements may result in a delay in treatment of fetal anemia. Unless additional concerns regarding fetal health and a potential need for imminent delivery are identified (i.e. fetal hydrops), deferring antenatal corticosteroids until after further evaluation for possible intrauterine transfusion is recommended to prevent this delay.[27]

eTable 4. Good Practice Points and Rationales

Recommendation 5: We recommend for women undergoing intrauterine transfusions in pregnancy for the treatment of HDFN, intrauterine transfusions should be continued until the end of the 35th week of gestation unless there are technical limitations to undertaking the procedure.	
Practice point	**Rationale**
5.1: Intrauterine transfusions should be performed proximate to resources for immediate delivery by Cesarean section when there is a shared patient/physician decision for immediate delivery for fetal indications (*95.1% Agreement).*	Vascular access to the fetus can result in vasospasm of vessels or umbilical cord hematoma resulting in acute fetal bradycardia. In a recent study of 35 patients undergoing IUTs after 34 wGA, 2 cases were associated with the need for emergent delivery with both infants surviving intact.[30]
5.2: Delivery should be scheduled 2-3 weeks after the final intrauterine transfusion. *95.1% Agreement*	Same as overall rationale for recommendation 5.
5.3: Ideally cordocentesis and intrauterine transfusions should be undertaken by an experienced operator at a center with proper access to blood banking and neonatal services. *97.6% Agreement*	The intrauterine procedure requires specialized skills in ultrasound-directed needle placement. In addition, the procedure requires coordination with multiple disciplines including, fetal medicine, anesthesiology and blood banking. An analysis of the learning curve of four operators at one referral center found that between 30 and 50 procedures were needed to obtain clinical proficiency. Ten procedures annually were suggested to maintain competency.[31]
5.4: Delayed umbilical cord clamping at the time of delivery can still be practiced in pregnancies affected by HDFN (*92.7% Agreement).*	Fetal blood remaining in the placental circulation can be auto-transfused to the fetus by delaying the time from delivery to cord clamping. This has the potential to reduce the incidence of newborn fetal anemia and the need for simple transfusions. A randomized study of 70 infants born to alloimmunized patients found a higher hematocrit (4.9%; 95% CI: 0.6-9.1%) at 2 hours of age with no increase in the duration of phototherapy or the need for exchange transfusions.[32]

eTable 4. Good Practice Points and Rationales

Recommendation 6: We recommend that women with a current or previous pregnancy with red cell antibodies known to cause hemolytic disease of the fetus and newborn (HDFN) regardless of titer who have not received an intrauterine transfusion, delivery should occur between 37 0/7 to 38 6/7 wGA.	
Practice point	**Rationale**
6.1: Red cell alloimmunization is an indication for weekly antenatal testing which should begin by 32 wGA. *85.4% Agreement*	Current monitoring for fetal anemia involves the use of the peak systolic velocity of the middle cerebral artery by Doppler ultrasound. Due to a false positive rate of 10% after 35 wGA, some authors have advocated that MCA-PSV has a limited value in late gestation.[29] Other methods of antenatal testing may be reassuring to both the patient and the physician and allow for prolongation of the pregnancy in the event of a minimal elevation in the MCA-PSV.
6.2: If the fetus is known to be antigen negative by prenatal testing, routine obstetrical care should be considered. *100% Agreement*	cffDNA is an accurate predictor of the red cell antigen status of the fetus (see rationale for recommendation #1). If the fetus is antigen negative, it is not at risk for fetal anemia or other complications of HDFN.
6.3: If the fetal antigen status is unknown, then delivery should occur between 37 0/7 to 38 6/7 wGA. *90.2% Agreement*	Same as overall rationale for recommendation 6.
6.4: Due to the presence of maternal antibodies, performing a maternal crossmatch for red cell units prior to delivery may be advantageous if there is an acute need for maternal or neonatal blood. In some cases, this may involve a planned delivery where there is a higher level of obstetrical and neonatal care available. *100% Agreement*	The presence of maternal antibodies may restrict ready access to blood products in the event of acute maternal hemorrhage. In addition, the transplacental passage of maternal antibodies to the fetus will result in their presence in the neonate. Should the neonate require blood for simple or exchange red cell transfusions, the red cell unit will need to be compatible with the maternal antibodies. This practice point coincides with the second recommendation from the pediatric/neonatal subgroup that participated in our Delphi process in the development of guidelines.
6.5: Red cell alloimmunization is not an indication for Cesarean delivery. *95.1% Agreement*	There are very little data to recommend the mode of delivery in cases of HDFN. A review of newborn cases of HDFN in the U.S. between 1996-2010 revealed a rate of Cesarean delivery of 30.6% as compared to 20.9% for healthy newborns.[33] However 78% of the cases in this survey included cases of HDFN secondary to ABO incompatibility. A Delphi survey of 107 experts in the management of HDFN from 25 countries reached a 98.7% consensus that route of delivery should be determined by the usual obstetrical indications.[15]
6.6: Neonatal consultation prior to delivery should be considered to develop a plan of management for the newborn. *100% Agreement*	Infants born to red cell alloimmunized mother may require simple blood transfusions to correct anemia or the initiation of phototherapy to treat hyperbilirubinemia. Communication between the obstetrical and neonatal service allows for coordinated care of these high-risk infants.
6.7: Evaluation of cord blood for blood type/cognate antigen, Direct antiglobulin test, hemoglobin/ hematocrit, reticulocyte count, and total bilirubin may be useful to guide the need for early phototherapy in the neonate. *100% Agreement*	Obtaining initial laboratory testing on cord blood allows for baseline information to better inform neonatal management decisions in cases of HDFN. The need for an acute blood transfusion to correct anemia or the early initiation of phototherapy can be guided by these laboratory values.

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